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Emily Kathleen Steinmetz
University of Louisville

THE EFFECT OF CAFFEINE ON FECUNDABILITY: DIFFERENCES IN COFFEE, TEA, AND COLA CONSUMPTION

By

Emily Kathleen Steinmetz
B.A., Bellarmine University, 2005

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Emily Kathleen Steinmetz
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A Thesis Approved on

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By the following Thesis Committee:

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Thesis Committee Director
Kira Taylor, PhD

_____
Second Committee Member
Anne Wallis, PhD

_____
Third Committee Member
Maiying Kong, PhD

DEDICATION

This thesis is dedicated to my parents

Alan Lawrence Steinmetz

and

Joetta Shuffett Steinmetz

who have always believed in me

and to my husband

Thomas John Reece

who makes me believe in myself.

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ABSTRACT

THE EFFECT OF CAFFEINE ON FECUNDABILITY

Emily K. Steinmetz

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This study examined whether intake of caffeinated beverages (coffee, tea, and cola) was associated with fecundability (time to pregnancy) in a prospective cohort study. Data from 470 women from the Mount Sinai Study of Women Office Workers (1990-1994) were analyzed. Intake of coffee, tea, cola, and other variables were recorded in daily diaries and calculated as menstrual cycle level means for up to 20 cycles. Pregnancy was assayed using hCG and confirmed by physician diagnosis. The associations of caffeinated beverages with the probability of becoming pregnant during a given cycle were determined using discrete survival analysis, adjusted for potential confounders. Overall caffeine intake was not significantly associated with fecundability. Moderate intake of coffee, tea and cola was associated with increased fecundability, and high intake with decreased, though most associations were not statistically significant. Moderation in caffeinated beverage consumption appears to be important for women who are trying to conceive.

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INTRODUCTION

Overview

Caffeine is a commonly consumed stimulant that is found in tea, coffee, soda, chocolate, and some medications (1, 2). There have been many studies investigating whether caffeine is associated with fecundability, spontaneous abortion, and menstrual characteristics (1-18). These studies have been somewhat contradictory, with some results that indicate a positive and negative association between caffeine and reproductive outcomes, and some studies showing no association at all (19).

Biological Mechanisms: Fecundability

Fecundability is the likelihood that a woman will become pregnant during a menstrual cycle (17). The mechanisms by which caffeine might affect fecundability are not entirely clear, although there have been some studies that have provided some insight (1, 4-7, 11-17, 20, 21). There is considerable evidence linking caffeine consumption to altered levels of reproductive hormones, which may contribute to fecundability. For example, estradiol is a hormone that stimulates the growth of the uterine lining and triggers the hormonal cascade that leads to ovulation (22). Caffeine intake was positively associated with estradiol levels in Lucero and associates 2001, but negatively associated with estradiol in Kotsopoulos and associates 2009 (23, 24). Schliep and associates 2012

found caffeine and estradiol to be negatively associated in white women, but positively associated in Asian women (25). A decrease in estradiol could inhibit ovulation and the development of the uterine lining, while an increase could make ovulation and uterine lining development more likely (22).

Another important hormone is progesterone. Progesterone prepares the lining of the uterus to accept and support a pregnancy and maintains the lining once a pregnancy has been established (22). Kotsopolous and associates 2009 found caffeine intake and progesterone levels to be positively associated, which could increase the likelihood of establishing and maintaining a pregnancy (22, 24).

There is some evidence that the hormonal changes seen with caffeine consumption could also alter menstrual cycle characteristics (10, 12, 13). Shorter menstrual cycles are one potential effect of caffeine consumption (16). A study published in 2006 by Small and associates reported that menstrual function was associated with changes in fecundability odds ratios and spontaneous abortion odds ratios (26). More specifically, shorter menstrual cycles were negatively associated with fecundability, and menstrual cycles of shorter and longer length were positively associated with spontaneous abortion (26). Therefore, shorter menstrual cycles may be a mechanism by which caffeine could reduce fecundability.

Caffeine may also act directly on oocytes. Caffeine has been shown to be inversely associated with both oocyte aging and oocyte maturation *in vivo,* but have the opposite effect *in vitro* (21, 27). Maturation of the oocyte is beneficial when trying to conceive, but aging causes the oocyte to begin to degrade and becomes less viable (27).

So, caffeine *in vivo* may be beneficial in the maturation of the oocyte, but deleterious once the oocyte is mature and begins to age (21, 27).

Biological Mechanisms: Pregnancy

Caffeine may also affect the development of an existing pregnancy. Wu and associates 2015 found that caffeine reduces the blood leptin levels in the fetus and placenta in rat pregnancies, which can impair fetal growth (28). Indeed, Bakker and associates 2010 reported that pregnant women who consumed the caffeine equivalent of six or more cups of coffee were more likely to give birth to babies who were small for gestational age (29). Hatzi and associates 2015 demonstrated that caffeine could induce asymmetric cell division of peripheral lymphocytes *in vitro* (30). The errors in chromosome distribution that can occur with asymmetric divisions could impair the viability of a pregnancy (30).

Animal Studies

There have been numerous animal studies that have demonstrated negative reproductive effects of caffeine (2, 16, 21, 31). For example, Yadegari and associates 2016 demonstrated that caffeine injections were associated with reduced numbers of implantations and live births in rats (18). There have also been animal studies that found no association between caffeine and pregnancy outcomes, such as spontaneous abortion, implantation and live births (21, 31). Ratnasooriya and associates 2009 reported not finding any effects of oral intake of Sri Lankan black tea on the number of implantations and live births in rats (31). The previously mentioned potential effects of caffeine on

oocyte maturation in vivo and in vitro were also conducted in an animal model; in this case, it was a mouse model (21).

Human Studies: Fecundability

A few studies have been published that found an association between caffeine intake and fecundability (13, 17, 19). More studies have been published that did not find any association (1, 3, 11, 12, 15). It is important when reviewing literature to examine studies that both did and did not find an association between the exposure and outcome of interest as this can be informative as to potential controversies within the field and can also highlight discrepancies between studies that reported different results.

One of the earliest studies that suggested that caffeine consumption negatively associated with fecundability was Wilcox and associates (17). The study started with 221, women who were trying to get pregnant and followed the 104 who did not conceive in the first three months for an additional three months or until they became pregnant. Information on caffeine consumption was collection upon entry, at three months, and at six months. The caffeine sources considered were brewed coffee, instant coffee, tea and caffeinated sodas (mg/day). The investigators found that women who consumed the greater than 3150mg of caffeine per month had significantly lower fecundability when compared to those who consumed less (OR = 0.53, 95% CI = [0.35-0.79]). The negative association was still observed when caffeine sources were divided into coffee (>1000mg caffeine/month: OR = 0.61, 95% CI = [0.42-0.90]) and non-coffee beverages (>1000mg caffeine/month: OR = 0.63, 95% CI = [0.43-0.93]). There was also a negative dose response, with higher levels of caffeine consumption associated with lower fecundability (17).

Wilcox and associates 1998 (17) is the study that spurred much of the research into whether caffeine could affect fertility. It should be noted that only coffee was singled out for individual analysis. The study could have been even more informative had it not grouped tea and soda consumption together in the same group. The sample size was also relatively small, which could have biased the results by exaggerating the relationship between caffeinated beverages and fecundability. The inclusion of just the 104 participants who had not conceived by three months may have depressed the fecundability of the study, because they were likely a subfecund group. In light of these shortcomings, it is clear that further research was needed in this area. A few of the studies that followed are summarized below.

After Wilcox and associates (17), another study that reported an association between caffeine intake and fecundability was Jensen and associates (13). This study followed 430 Danish couples, between 20 and 35 years of age, who were attempting to become pregnant for the first time. The researchers followed the couples until pregnancy or for six menstrual cycles. Data on smoking, alcohol intake and daily caffeine intake were collected each month. The caffeine sources that were included were coffee, tea, soda, chocolate bars and chocolate containing beverages (mg/day). The study found a nonsignificant decrease in fecundability in nonsmoking women who consumed caffeine from non-coffee sources (OR = 0.43, 95% CI = [0.16-1.13]) and a significant decrease in fecundability in women who smoked and consumed caffeinated coffee and no other caffeine source (OR = 0.34, 95% CI = [0.12-0.98]) when compared to women who did not smoke or consume coffee. When broken into specific caffeine sources, the only

source that significantly decreased fecundability was coffee, and that was only among smoking women, as previously mentioned (13).

It is noteworthy that this study suggests that there may be an interaction between coffee and cigarettes (13). Smoking is often controlled for in studies examining caffeine consumption because individuals who smoke also often drink caffeinated beverages, particularly coffee (19). It might be worthwhile to conduct further studies to investigate the possible biological interaction between coffee and cigarette exposure. This was also one of the two studies found that included chocolate bars as a source of caffeine, and the only study to include chocolate containing beverages (13, 32).

Another study that found a significant interaction between caffeine and another exposure was Hakim and associates 1998 (11). This study included 124 women between the ages of 24 and 41 years who worked in semiconductor manufacturing. The participants were followed until pregnancy. Not all women became pregnant during the study, but there was no mention of how long the participants, in general, were followed, or a time period or number of menstrual cycles after which women who did not conceive were dropped from the study. Data on caffeine intake was collected every month. Caffeine sources included were coffee, tea and caffeinated soft drinks (mg/day). The authors reported a nonsignificant negative association between caffeine consumption and conception rates (OR = 0.48, 95% CI = [0.26-1.35] in nonsmoking women who consumed 101-300mg of caffeine per day, and OR = 0.83, 95% CI = [0.34-2.01] in nonsmoking women who consumed 301mg or more of caffeine per day). The negative association was significant in women who also drank alcohol (OR = 0.44, 95% CI = [0.23-0.86] for less than 101mg caffeine, and OR = 0.26, 95% CI = [0.13-0.52] for

greater than 100mg caffeine). Alcohol alone also had a significant negative association with conception rates (11).

The results from this study indicate that there may be a biological interaction between alcohol and caffeine exposures within the body (11). People who drink caffeine are more likely to also drink alcohol than those who do not, which is why alcohol consumption is usually controlled for in studies of the effects of caffeine (2, 10, 32). This study indicates that studies on the interaction between caffeine and alcohol should be pursued. It should also be noted that this study did not individually analyzed the different sources of caffeine (11).

Among the fecundability studies that did not find any association with caffeine was Wesselink and associates 2016 (16). This study included 2135 women, 21-45 years old, who were trying to conceive. The women were followed for twelve months or until they became pregnant. Caffeine intake and pregnancy status data were collected every eight weeks. Data was collected on the following caffeine sources: coffee, decaffeinated coffee, black tea, green tea, white tea, soda and energy drinks (mg/day). Caffeine was not associated with fecundability (OR = 0.99, 95% CI = [0.88-1.10 for 100-199mg], OR = 0.93, 95% CI = [0.78-1.11, 200-299mg], and OR = 0.90, 95% CI = [0.69-1.18] for greater than 300mg, when compared to less than 100mg). When caffeine sources were analyzed individually, most sources had nonsignificant negative associations with fecundability, while green tea and energy drinks did not have any association. For example, black tea had a fecundability OR of 0.89, 95% CI = [0.53-1.48] and energy drinks had an OR of 0.95, 95% CI = [0.77-1.17] (16).

This was the only study to break tea into black, green, and white teas. This could be important because different types of tea appear to have different caffeine concentrations (16). The researchers also made an effort to determine what brands of soda and energy drinks that the participants were consuming, because different brands have different caffeine contents. It also split sodas into regular and diet because they sometimes have different amounts of caffeine. Furthermore, it is one of the only studies to collect data on caffeine containing medications. While the addition of caffeine from medications did not significantly influence the model, it is still something that should probably be kept in mind in future studies (16).

Another study that reported no association between caffeine and time to pregnancy was Taylor and associates 2011 (15). The study followed 470 women office workers, between 18 and 40 years of age, who were at risk for becoming pregnant. The women were followed until pregnancy or twelve months. The participants filled out daily diaries on their caffeine, cigarette, and alcohol consumption. Caffeine sources included were coffee, tea and cola (mg/day). The study found no effect of caffeine (OR = 1.02, 95% CI = [0.67-1.56] for 150-300mg and OR = 0.89, 95% CI = [0.58-1.38] for greater than 300mg) on fecundability (15).

This was the only study reviewed that collected daily information on caffeine consumption (15). Daily data can allow investigators to take changes in caffeine consumption over time into consideration, instead of relying on a small window of consumption that may or may not be representative of normal caffeine intake patterns (19). It could have been useful to have split the daily caffeine intake data into coffee, tea

and cola for separate analyses. This would allow for the detection of any source specific effects.

Hatch and associates 2012 also did not find an association (12). The study included 3,628 Danish women, aged 18 to 40 years, who were planning a pregnancy. The women were followed for twelve menstrual cycles or until they became pregnant or started fertility treatment. Participants filled out questionnaires about caffeine consumption upon entry into the study and every two months during participation. The caffeine sources included were coffee, decaffeinated coffee, tea and cola (mg/day). Green tea was grouped with herbal tea and was therefore not included as a source of caffeine. Overall caffeine intake was not associated with fecundability (OR = 0.98, 95% CI = [0.88-1.10] for 100-199mg, OR = 1.07, 95% CI = [0.92-1.24] for 200-299mg, and OR = 1.04, 95% CI = [0.90-1.21] for greater than 300mg). Tea was associated with a nonsignificant increase in fecundability (OR = 1.27, 95% CI = [0.98-1.64] for more than two daily servings) and soda with a nonsignificant decrease in fecundability (OR = 0.48, 95% CI = [0.21-1.13] for more than three daily servings) (12).

This study was another study that it split sodas into regular and diet when determining the amount of caffeine that each contributed, thus allowing for greater accuracy (12). Diet sodas were counted as contributing 15mg more caffeine per serving than regular sodas. However, green tea was grouped together with herbal tea and not counted as a caffeine source, which could reduce the accuracy of the caffeine consumption estimate (12).

Among the studies that examined caffeine and fecundability, the three that found an association had fairly small sample sizes and followed participants for shorter time periods (or did not specify the study period) (11, 13, 17). The studies that did not find an association tended to have larger sample sizes and followed participants for up to twelve months or cycles (12, 15, 16). Both study period and size have the potential to affect the results of a study and should be taken into consideration when reviewing published studies and when designing new studies.

Human Studies: Spontaneous Abortion

Another indicator of the potential effects of the caffeine exposure on reproduction is spontaneous abortion (2, 3, 8, 10). Only one of the studies on spontaneous abortion reported a significant association between the outcome of interest and caffeine (10). Hahn and associates 2015 included 5,132 Danish women, 18 to 40 years old, who became pregnant during a time to pregnancy study (10). The participants were followed until they became pregnant. Hospital and birth registries were accessed to determine the outcomes of pregnancies. Data was collected on caffeinated coffee, decaffeinated coffee, black tea and caffeinated cola consumption (mg/day). Exposures were recorded every two months before pregnancy and in an additional questionnaire after pregnancy detection. Consumption of caffeine before pregnancy was not associated with spontaneous abortion (HR = 1.00, 95% CI = [0.81-1.23] for 100-299mg, HR = 1.19, 95% CI = [0.96-1.49] for 200-299mg and HR = 1.09, 95% CI = [0.89-1.33] for greater than 300mg), but consumption during early pregnancy was positively associated with spontaneous abortion (HR = 1.62, 95% CI = [1.19-2.22] for 100-199mg, HR = 1.49, 95% CI = [1.03-2.13] for

200-299mg, and HR = 1.23, 95% CI = [0.61-2.46] for greater than 300mg). No one caffeine source was specifically associated with spontaneous abortion (10).

This is another study that grouped green tea and herbal tea together, which meant that green tea could not be included as a source of caffeine (10). This could possibly underestimate caffeine intake. It is noteworthy that alcohol consumption was not found to be a confounder in this study, as there is evidence in other studies of an association between alcohol consumption and caffeine consumption (2, 10, 32).

Among the spontaneous abortion studies that did not find an association was Dlugosz and associates (8). In this study 2,967 women were followed from their first trimester of pregnancy until they gave birth or lost the pregnancy. Participants were interviewed upon enrollment about their caffeine intake during the first month of pregnancy. Potential caffeine exposures included coffee, tea and soda (mg/day). A positive nonsignificant association was observed between caffeine and spontaneous abortion (OR = 1.75, 95% CI = [0.88-3.47] for more than 300mg). When divided into the three different caffeine sources, coffee was the only source that did not include unity at all consumption levels (OR = 2.63, 95% CI = [1.25-5.34] for three or more cups per day). Tea had a nonsignificant positive association with spontaneous abortion (OR = 2.33, 95% CI = [0.92-5.85] for three or more cups per day) (8).

A shortcoming of this study is that it required some women to retrospectively report caffeine consumption from the first month of pregnancy (8). This could result in recall bias in women who were past their first month of pregnancy at the time of the interview.

Another spontaneous abortion study that did not find an association was Fenster and associates 1997 (2). 5,144 pregnant women were recruited for the study when they scheduled their first prenatal checkups. The women were followed to determine whether their pregnancies were carried to term or resulted in spontaneous abortion. Information on caffeine consumption during the first trimester was collected upon enrollment. Caffeine sources included were coffee, tea and soda (mg/day). Nausea was significantly associated with miscarriage, but was left out of the model because it did not appear to be a confounder. Caffeine consumption was not associated with spontaneous abortion (OR = 1.25, 95% CI = [0.90-1.73] for greater than 300mg before pregnancy and OR=1.29, 95% CI = [0.8-2.06] for greater than 300mg during the first trimester). However, consumption of three or more cups of decaffeinated coffee during the first trimester was significantly associated spontaneous abortion (OR = 2.37, 95% CI = [1.22-4.60]) (2).

The association between decaffeinated coffee and spontaneous abortion indicates that there may be other substances besides caffeine in coffee that can affect pregnancy outcomes (2). Because the association with spontaneous abortion was seen in decaffeinated coffee and not caffeinated coffee, the authors suggested that there may be a difference in the chemical makeup of decaffeinated coffee (2). It might be worthwhile to conduct a study comparing the chemical makeup of caffeinated and decaffeinated coffee.

There do not appear to be major differences in the designs of the study that found an association between caffeine and spontaneous abortion and the two studies that did not. All had large sample sizes and individually analyzed different caffeine sources, although the caffeine intake recorded in Dlugosz and associates 1996 may have been affected by recall bias (2, 8, 10).

Human Studies: Ovulation and Menstrual Function

The potential effects of caffeine intake on ovulation and menstrual function have also been studied (6, 9). As previously mentioned, menstrual characteristics may have a significant effect on fecundability and spontaneous abortion (26). One particularly large study was published by Chavarro and associates in 2009 (6). In this study, 18,555 women attempting pregnancy were followed for eight years. The cohort of women was drawn from the Nurses' Health Study II. Data on caffeinated beverage consumption was collected every four years. Caffeinated beverages included coffee, tea, cola and non-cola carbonated beverages (mg/day). Overall caffeine intake was not associated with ovulatory infertility (OR =1.07, 95% CI = [0.78-1.47] for 161-332mg and OR = 0.86, 95% CI = [0.61-1.20] for more than 333mg), but high consumption of caffeine containing soft drinks was positively associated (OR =1.47, 95% CI = [1.09-1.98]) (6).

This was the largest of the reviewed studies and was noteworthy in its focus on ovulatory function. The study could help clarify the understanding of how caffeine could potentially affect fecundability (6). It could be interesting to investigate what it is about caffeinated soft drinks that actually affects ovulatory fertility.

Another study that examined the potential association between caffeine and menstrual cycle characteristics was Fenster and associates 1999 (9). The study followed 403 women between 18 and 39 years old. The participants kept daily diaries on menstrual occurrences, such as bleeding. They also collected daily urine samples to be tested for sex hormones and their metabolites. Caffeine consumption data was collected upon enrollment and included coffee, tea and soda (mg/day). Caffeine intake of greater than

300mg per day had a non-significant negative association with anovulation (OR=0.36, 95% CI = [0.04-3.36]) and a non-significant positive association with short menstrual cycles (OR = 2.00, 95% CI = [0.98-4.06]). A short menstrual cycle was defined as a cycle that was less than or equal 24 days. No association was found between caffeine and short luteal phases, long follicular phases, or long cycles (9).

This was another study with the potential to help clarify what aspect of the menstrual cycle caffeine might affect fecundability through. However, the study did not analyze coffee, tea and soda individually to determine whether there were any source specific associations with menstrual cycle characteristics (9). There is the potential that at least one of the sources had an individual effect that was masked by keeping all of the sources together in one group.

The two studies on ovulation and menstrual function did not find a significant association with caffeine in general, although Chavarro and associates did find an association with caffeinated soft drinks. While neither study was explicit about how long the participants were followed, the women in the Chavarro study were followed for at least four years (6, 9). More research in this area may be warranted.

In light of human and animal studies such as these, The Food and Drug Administration has advised pregnant women to limit caffeine intake (3, 32). In spite of these recommendations there is still considerable debate as to whether caffeine really does have negative reproductive effects in humans, because the results from human studies have been inconsistent (19). Studies in human volunteers continue to be

conducted in an attempt to clarify whether there is an association, and if so, in what direction.

Discrepancies

It has been suggested that some of the discrepancies between studies may be due to reverse causality (19). For example, women who report nausea are less likely to experience a spontaneous abortion (2, 10). Fenster and associates 1997 found that women who experience nausea had an odds ratio for spontaneous abortion of 2.6 (95% CI = [2.1-3.2]) (2). These women are also more likely to decrease their caffeine intake due to the nausea (10). A positive association between caffeine consumption and spontaneous abortion may really be a reflection of the inverse association between nausea and spontaneous abortion (19). It is also worth considering that women may change their caffeine consumption upon discovering that they are pregnant, whether they experience nausea or not. Chen and associates published a study in 2014 in which women who had recently given birth to healthy children where asked about their caffeine consumption before and after they knew that they were pregnant. Most of the women in the study either reduced their intake or stopped drinking caffeinated beverages altogether once they knew that they were pregnant (32). This is one reason that daily data on caffeine consumption can be very important as it allows these changes in intake to be accounted for.

Studies also did not always control for, or even consider, the same potential confounders. For example, Wilcox and associates 1988 was the only study to consider marijuana as a confounder and Wesselink and associates 2016 was the only study that

included sleep duration as a confounder (16, 17). These differences could strongly influence the outcomes of the analyses for each study and decrease how well results can be compared across studies.

Another potential source of discrepancy between studies is the use of different measures to determine caffeine intake. Some studies only collected data on coffee consumption (19). Many included coffee, tea and cola (1-3, 6, 8-12, 16). Others also included chocolate or energy drinks, and very few account for caffeine containing medications (13, 16). In most of these cases, caffeine consumption was self-reported and potentially subject to reporting bias (19). Other studies based their measurements of caffeine exposure on caffeine and caffeine metabolites found in the urine, or other bodily fluids (3, 19). Studies also differed in how often they collected data on caffeine exposure. Some only collected data upon enrollment, others collected data every few months, and still another had participants fill out daily diaries on their caffeine intake (8-10, 12, 15). An issue with data collection being restricted to the enrollment interview is that it does not account for changes in caffeine consumption over time (19). As previously mentioned, it has been shown that women often change their caffeine intake upon discovering that they are pregnant (32).

There were also differences in how much caffeine was attributed to a serving of each caffeine source. For example, Hakim and associates 1998 attributed 100mg of caffeine to each serving of coffee, 50mg to tea and 40mg to soft drinks, while Taylor and associates 2011 attributed 150mg to coffee, 55mg to tea and 45mg to colas (11, 15). Wesselink and associates 2016 went as far as to have separate caffeine values for black, green, and white tea (40mg, 20mg and 15mg, respectively), and to look up the caffeine

content of different brands of soft drinks and energy drinks (16). These differences could change the estimates of caffeine exposure, which could make comparisons between studies less valid.

Conclusion

Taken as a whole, the reviewed literature indicate that there is not an association between overall caffeine consumption and fecundability or pregnancy outcomes such as spontaneous abortion. Further studies are still needed to expand upon existing research and to examine individual caffeine sources more carefully. Based on the studies reviewed here, future studies in this area may want to consider including nausea during the first trimester, alcohol and smoking as confounders, as well as consulting published literature for other relevant confounders, collecting daily caffeine intake data for at least coffee, tea and soft drinks (with further categories and subcategories possible), determining the best caffeine estimates for each caffeine source by consulting published literature or running analytical tests, and analyzing caffeine sources together and individually to detect any association with fecundability.

The purpose of this study is to address the question of whether sources of caffeine differ in their effects on fecundability, using caffeine data collected on a daily basis. The specific aims are 1) to determine whether caffeine is associated with fecundability, 2) to determine whether coffee, tea and cola are associated with fecundability, and 3) to determine whether there are interactions between coffee, tea and cola consumption when examining their effects on fecundability.

METHODS

Study Population

The Mount Sinai Study of Women Office Workers (MSSWOW) included 470 women between the ages of 18 and 40 who worked in offices in New England from 1990 to 1994. To be eligible for the study, women had to be sexually active with an unvasectomized partner and could not be currently pregnant, infertile or using hormonal birth control or intrauterine devices. To be included in this analysis of caffeine and fecundability, the women had to have recorded information on their daily intake of coffee, tea and cola. All 470 women had data on overall caffeine consumption, but only 460 had data on coffee, tea and cola. Women were asked to participate in the study until pregnancy or twelve months, whichever came first. However, some women elected to stay in the study longer (up to 19 months). The mean follow-up time was 8 cycles.

Data Collection

Upon intake, data were collected on age, body mass index (BMI), race, marital status, parity, prior use of oral contraceptives (OC), education and desire to become pregnant. Daily diaries were also filled out and included computer use, cigarette and alcohol use, caffeinated beverages, stress, menstruation and intercourse with or without a protection. Intercourse without nonhormonal birth control, such as a condom or sponge,

during the estimated ovulatory window (21 to 12 days before the next menstruation) was designated as unprotected sex. Diaries were mailed in by the participants at the end of each month. The women also collected urine samples on the first and second days of the menstrual cycle (the first day and second days of menstrual bleeding), or one week after the expected first and second days of the cycle if bleeding did not actually begin. Urine samples were stored in home freezers until they could be picked up for analysis.

Exposure

The daily diaries that the participants filled out included coffee, tea and cola consumption. Coffee and tea were measured in servings of 8 oz. cups and cola in 12 oz. cans.

Outcome

Pregnancy status was determined by assaying the urine samples for human chorionic gonadotropin (hCG), a biomarker that is expressed early in pregnancy. Two consecutive hCG readings above 0.25ng/mL during a menstrual cycle constituted a pregnancy. All pregnancy diagnoses were confirmed by the participants' physicians.

Variables

The variables collected fell into three categories: woman-level, cycle-level and daily level. Most woman-level variables were those collected upon intake and included age, race, BMI, marital status, past OC use, parity, education and desire to become pregnant. The woman-level cycle length variability was calculated for each woman from the lengths of all of her analyzed cycles. Woman-level variables were constant and did

not change over the course of the study. Cycle-level variables included bleed length and cycle length. These variables were calculated from daily diary entries on menstrual bleeding. Each cycle had an individually calculated bleed length and cycle length. Cycle variability, cycle length and bleed length had already been calculated and were included in the data set. Daily level data include overall caffeine intake (servings/day), cups of coffee and tea, and cans of cola; number of cigarettes smoked; number of alcoholic beverages consumed; unprotected sex (yes/no) and stress (on a scale from 1 to 4). Cycle-level variables for tea, coffee and cola were calculated from the daily data by taking the average of the daily values over the course of each cycle. The new cycle-level variables had one average value per cycle.

The variables used in the analysis were coded as categorical variables. Cycle-level exposure variables were assigned to categories as follows: mean servings of caffeine per day (0 to 1, >1 to 2, >2), mean servings of coffee per day (0, >0 to 1, >1), mean servings of tea per day (0, >0 to 1, >1), and mean servings of cola per day (0, > 0 to 1, >1).

Confounders

Potential confounders were chosen based upon a review of existing literature. Confounders considered included age, BMI, race, marital status, education, smoking, alcohol, unprotected sex, parity, menstrual cycle length and standard deviation, bleed length, past OC use, trying to conceive, stress and exercise. The potential for variables to confound the outcome were analyzed using a directed acyclic graph (DAG) and by subtracting potential confounders individually from the full multivariable model and observing whether the beta coefficients for coffee, tea and/or cola consumption

significantly changed (>10%) (Table 1). Variables that did not have a significant effect on the beta coefficients were not included in the model unless they were generally expected to be present in reproductive models. Examples include age and marital status.

Statistical Analysis

All statistical analyses were conducted using SAS v. 9.4 (Cary, NC). The associations between cycle-level means for caffeine, coffee, tea and cola and fecundability (risk of pregnancy in a given cycle) were analyzed using discrete survival analysis. Discrete survival analysis uses a discrete time variable (in this case, cycles) when examining the time to an event (pregnancy). It models the probability of conception in a particular cycle, conditioning on not having conceived in any previous cycle (it provides the conditional probability of failure in a particular cycle) (33). Pregnancy is the event; if a woman did not conceive during the study, she is censored at the time of study end or withdrawal. Cycle-level covariates and confounders were used for the discrete survival analysis where available, along with woman-level variables that had been collected at intake. 2,740 cycles were included in the analysis. One model examined the overall effect of caffeine; a second model examined the effects of tea, cola and coffee individually and simultaneously to mutually control for all three caffeine sources.

Product terms in the discrete survival analysis model were used to test for interactions between tea and cigarettes, tea and alcohol, coffee and cigarettes, coffee and alcohol, cola and cigarettes and cola and alcohol. In addition, the interactions of each source of caffeine with the others (e.g., interaction between tea and cola) were tested. Interactions were tested using the likelihood ratio test in which the chi-square statistic is

calculated by subtracting the -2 Log likelihood for the model with the interaction from the -2 Log likelihood for the model without the interaction. If the associated P-value was significant (<0.05) then the model was significantly improved by the addition of the interaction term and the term was kept in the model (Table 1).

Descriptive Statistics

Woman-level data were used for the descriptive statistics, including woman-level values for mean daily servings of alcohol, mean cigarettes per day, mean cycle length and mean bleed length. Tertiles for mean stress and fraction of days exercised in the woman level data had different cutoffs than in the cycle level data: means stress (0 to 1.75, >1.75 to 2.36, >2.36 to 4) and fraction of days exercising (0 to 0.09, >0.09 to 0.29, >0.29). Chi-square test *p*-values were calculated for the association between the variable of interest and the exposures (categories of woman level daily servings of caffeine, coffee, tea, cola). Fisher's exact test *p*-values were used when the expected values of at least 25% of the cells were <5. A *p*-value of less than 0.05 was considered significant.

Power Calculations

Power calculations were performed using SAS v. 9.4 (Cary, NC) (PROC POWER). The reference hazard (0.04) was calculated by dividing the total number of pregnancies (n=109) by the total number of cycles included in the study (n=2,740). Women were followed up for an average of 8 cycles. A sample size of 460 was used for the calculations to be conservative. Power was calculated for hazard ratios of 0.2 through 1.8 because there was a possibility that coffee, tea and cola could increase or decrease the hazard ratio for fecundability. 80% (0.8) power is generally accepted as the lower limit

for ability to detect effect sizes (hazard ratios, in this case). The calculations indicate that this study was adequately powered to detect hazard ratios ≤ 0.5 and ≥ 1.6 (Table 2).

Institutional Review Board Approval

The data collection was approved by the Institutional Review Board of Mount Sinai School of Medicine, NY, as well as the Institutional Review Board of Emory University, GA. The Institutional Review Board of the University of Louisville, KY approved the data analyses for this study (IRB 17.0158).

RESULTS

The majority of the 470 women in this study who contributed data on caffeine consumption were married (66%), non-Hispanic white (78%), had been educated beyond high school (83%), were non-smokers (61%), and drank alcohol (89%). Most of the women were between 25 and 41 years of age (91%) and a slight majority had BMI's between 20 and 25 (51%). At intake, 25% of participants said that they were attempting to become pregnant, and 38% conceived during the course of the study.

The median consumption of caffeinated beverages was 1.9 servings per day (IQR = 1.01, 2.80). Caffeine consumption was positively associated with cigarette smoking ($p < 0.006$) and alcohol ($p = 0.001$), non-Hispanic white race ($p = 0.02$) and being married ($p = 0.04$). It was negatively associated with highest education ($p = 0.006$) (Table 3).

460 of the 470 women contributed data on coffee, tea and cola consumption. The median consumption of coffee was 0.72 cups per day (IQR = 0.02, 1.64). Coffee consumption was positively associated with age ($p = 0.001$), cigarette smoking ($p = 0.0003$), alcohol ($p < 0.0001$) and history of oral birth control ($p = 0.03$), and negatively associated with trying to conceive ($p = 0.01$). White race was positively associated with coffee consumption and black race was negatively associated ($p = 0.0001$) (Table 4).

Among the women who contributed data on tea consumption, the median reported tea consumption was 0.07 cups per day (IQR = 0.01, 0.38). Married and single women were more likely consume moderate levels of tea (>0 to 1 cup per day), while women who were separated, divorced or widowed were more likely to have no consumption or high consumption (0 or >1 cups per day) ($p = 0.02$). Tea consumption was negatively associated with bleed length ($p = 0.04$) (Table 5).

The median consumption of cola was 0.22 cans per day (IQR = 0.04, 0.67). Cola consumption was positively associated with BMI ($p = 0.03$), and was negatively associated with education ($p = 0.01$) (Table 6).

Two models were run with fecundability as the dependent variable. The primary predictive variable in the first model was caffeine (0 to 1, >1 to 2, >2 daily servings). Coffee, tea and cola (0, >0 to 1, >1 daily servings) were the primary predictive variables in the second. Each model controlled for age at baseline (19 to 24, 25 to 29, 30 to 34, 34 to 41 years), BMI at baseline (<20, ≥20 to 25, >25 to 30, >30 kg/m^2), race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), marital status at baseline (single, married, other (divorced, widowed, separated)), trying to get pregnant at baseline (yes, no), mean smoking per cycle (0, >0 to <10, 10 to ≤20, >20 daily cigarettes), mean alcohol intake per cycle (0, >0 to 1, >1 daily servings), unprotected sex during a cycle's ovulatory window (yes, no), cycle length standard deviation (tertiles: 0 to 2.09, >2.09 to 4, >4 days) and exercise per cycle (tertiles: 0 to 1.69, >1.69 to 2.26, >2.26 hours per week). There was a significant negative correlation between intake of coffee and tea, and between the intake of coffee and cola. In light of this, the models for coffee, tea and cola controlled for the other caffeinated drinks; the coffee fecundability odds ratio (FOR) was

adjusted for tea and cola, the tea FOR was adjusted for coffee and cola, and the cola FOR was adjusted for coffee and tea. The terms for interactions between coffee, tea and cola with regards to fecundability were not significant, therefore the interactions were left out of the final model. Interactions between the individual caffeinated beverages and average weekly cigarette and alcohol consumption were also examined. The interactions did not significantly affect fecundability and were left out of the final model.

FORs were calculated for overall caffeine, coffee, tea and cola, with the lowest serving category as the reference (Tables 7-10). FORs indicate the relative odds that pregnancy will occur during any menstrual cycle as compared to the reference group. Overall caffeine intake was associated with a nonsignificant decrease in fecundability of approximately 40% at greater than one to two servings per day and approximately 30% at greater than two servings per day.

The FORs for coffee, tea and cola consumption showed the same nonlinear trends: greater than zero to one servings per day increased fecundability, whereas greater than one servings per day decreased fecundability. Tea consumption was not significantly associated with fecundability. Coffee was not significantly associated with fecundability at greater than zero to one servings per day, but was associated with a significant decline in fecundability at greater than one servings per day. Greater than zero to one servings of cola per day were associated with a significant increase in fecundability. Consuming greater than one servings of cola per day was not significantly associated with fecundability.

DISCUSSION

This study is consistent with previous research that demonstrated a lack of association between overall caffeine intake and fecundability (12, 15, 16). There was not a significant association between caffeine and time to pregnancy in this analysis. Like many studies, it also did not find an association between tea intake and fecundability (12, 15). However, it is one of the few studies, such as Wilcox and associates 1988, that found a decrease in fecundability with coffee consumption (11, 13, 17). High coffee consumption was significantly associated with a 64% reduction in the odds of becoming pregnant during a cycle. This was the only study to find a significant increase in fecundability with cola consumption. Moderate cola consumption was significantly associated with approximately twice the odds of becoming pregnant.

All three types of beverages displayed the pattern of an increase in fecundability with moderate consumption (>0 to 1 drink/day) and a decrease in fecundability with high consumption (>1 drink/day). The increase in fecundability with moderte tea, coffee, and cola consumption was unexpected based upon existing literature, although only the association with cola was significant (11, 13, 17). It is possible that there are components in these beverages, besides caffeine, that are contributing their associations with fecundability. It also may be the case that coffee and cola consumption are actually indicators of other behaviors that affect fecundability, such dietary or lifestyle patterns. We tried to control for lifestyle factors such as exercise and the use of cigarettes and

alcohol, but there may be residual confounding. Dietary data were not available to include in the analysis. This analysis indicates that that when consuming caffeinated beverages while attempting to conceive, moderation may be key.

A major strength of this study was the use of data that had been collected on a daily basis. This reduced the likelihood of recall bias being an issue and allowed for a more accurate estimate of the aforementioned covariates and exposures of interest for each cycle. In many studies, such as Fenster and associates 1999, data on caffeine intake was only collected upon enrollment (9). In others, such as Wilcox and associates 1998 and Hatch and associates 2012, data on caffeine consumption was collected at intervals of several months (12, 17). One measure of caffeine intake, or a few spaced months apart might not be as accurate due to changes in caffeine consumption that can occur during the course of a study.

Another strength was the use of hCG assays to determine pregnancy status. The assay can capture subclinical pregnancies that might have otherwise gone undetected. Pregnancies that were detected through the assay were confirmed by a physician. The use of the assay allowed for a more accurate estimation of time to pregnancy than a clinical diagnosis alone would have given.

This study had several limitations. One limitation is that cycle bleed length and exposures to coffee, tea, cola, alcohol, cigarettes, stress, exercise and unprotected sex were self-reported and could be subject to reporting bias. For example, participants may underreport behaviors that they perceive as socially undesirable, such as smoking and drinking. They may also overreport socially desirable behaviors, such as exercise.

Reporting errors may also occur as a result of poor recall, though this should be reduced if the participants filled out their diaries every day. These errors in reporting could lead to misclassification of exposure status.

Another potential source of bias is missing information. For example, there was some missing data on daily cigarette use, stress and exercise and baseline data on whether participants were trying to conceive. Cycles in which diary data was missing for the entire month had to be excluded from analysis (N = 269). It may be the case that there is something systematically similar among the women who did not provide this information, which would bias the results.

There also may be issues with the generalizability of the data. The study was restricted to women who worked in office settings. The results may be less generalizable if women who work in offices are systematically different than the general population. For example, women office workers could display different health behaviors and be exposed to different risk factors for low fecundability than women who stay at home or who work in other environments. Infertile worker effect may also be an issue in a study of office workers. Infertile worker effect results from more fertile women having already removed themselves from the workforce by having children and staying home to care for them. The women remaining in the workforce are more likely to have low fertility. The generalizability may also be affected by the time period during which the data was collected. Intake data was collected from 1990 to 1994, with an average follow-up time of 8 cycles. Patterns of caffeine beverage consumption have changed since the data for this study were obtained, making the results less generalizable for the current population.

Another potential issue is that not everyone in the study was trying to get pregnant. Only about 33% of the participants reported a desire to become pregnant at the beginning of the study. This may depress the fecundability compared to a study in which all participants are trying to conceive. Women who are trying to conceive may also differ in their exposures to health-related behaviors that affect fecundability.

The study also did not include other caffeine sources, such as chocolate, medications, energy drinks, or caffeinated herbal teas like yerba maté. Unaccounted for effects of these other caffeine sources could have affected the results of the analysis, particularly if consumption of any of these additional sources turned out to be correlated with the consumption of coffee, tea or cola.

CONCLUSION

All three types of caffeinated beverages displayed the same pattern: an increase in fecundability with moderate intake (>0 to 1 serving) and a decrease in fecundability with high intake (>1 serving). The overall trend suggests that moderation in consumption of caffeinated beverages may be important for women attempting to conceive. The results help clarify whether caffeinated beverages affect fecundability and contribute to the body of knowledge that is used to counsel women who are attempting to become pregnant. Future research could investigate whether the associations of moderate consumption of coffee, tea and cola with fecundability are due to other lifestyle choices made by people of moderate caffeinated beverage intake. We attempted to control for associations with other exposures that affect fecundability in this analysis; however, residual confounding may exist. Future research could also look into whether these beverages contain ingredients besides caffeine that affect time to pregnancy.

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APPENDIX

Table 1

Confounding in the Coffee, Tea, and Cola Model

	Coffee 1å2 beta (% Δ)	Coffee 1å3 beta (% Δ)	Tea 1å2 beta (% Δ)	Tea 1å3 beta (% Δ)	Cola 1å2 beta (% Δ)	Cola 1å3 beta (% Δ)	N cycles used
Full model	0.2837	-1.0748	0.3547	-0.3547	0.7268	-0.2249	2697
After removal of:							
Age	0.266 (6.2)	-1.0856 (1.0)	0.3405 (4.0)	-0.3208 (9.6)	0.6945 (4.4)	-0.2936 (30.5)	2697
Body mass index	0.0624 (78.0)	-1.1989 (11.5)	0.0897 (74.7)	-0.3825 (7.8)	-0.00933 (101.3)	-1.1147 (395.6)	2697
Race	0.2439 (14.0)	-1.0256 (4.6)	0.3831 (8.0)	-0.3087 (13.0)	0.7001 (3.7)	-0.2081 (7.5)	2697
Marital status	0.2818 (0.7)	-1.0713 (0.3)	0.3413 (3.8)	-0.3679 (3.7)	0.7223 (0.6)	-0.2136 (5.0)	2697
Highest education	0.2754 (2.9)	-1.0747 (0.0)	0.3671 (3.5)	-0.3225 (9.1)	0.7008 (3.6)	-0.2473 (10.0)	2697
Cigarettes	0.2932 (3.3)	-1.0315 (4.0)	0.4112 (15.9)	-0.3117 (12.1)	0.6837 (5.9)	-0.23 (2.3)	2720
Alcohol	0.2746 (3.2)	-1.0797 (0.5)	0.3087 (13.0)	-0.4204 (18.5)	0.666 (8.4)	-0.2816 (25.2)	2697
Unprotected sex	0.2271 (20.0)	-1.1321 (5.3)	0.3115 (12.2)	-0.4682 (32.0)	0.7585 (4.4)	-0.1772 (21.2)	2697
Parity	0.2856 (0.7)	-1.0804 (0.5)	0.3479 (1.9)	-0.3511 (1.0)	0.7343 (1.0)	-0.2055 (8.6)	2697
Cycle length	0.2928 (3.2)	-1.0612 (1.3)	0.3708 (4.5)	-0.3402 (4.1)	0.7307 (0.5)	-0.2219 (1.3)	2697
Bleed length	0.2731 (3.7)	-1.0857 (1.0)	0.3555 (0.2)	-0.3825 (7.8)	0.7383 (1.6)	-0.2033 (9.6)	2697
Cycle standard deviation	0.3844 (35.5)	-1.0064 (6.4)	0.491 (38.4)	-0.1829 (48.4)	0.6529 (10.1)	-0.2972 (32.1)	2731
Oral contraceptive use	0.2806 (1.1)	-1.08 (0.5)	0.3527 (0.6)	-0.3677 (3.7)	0.7212 (0.8)	-0.2244 (0.3)	2697
Trying to get pregnant	0.2842 (0.2)	-1.1255 (4.7)	0.3114 (12.2)	-0.4119 (16.1)	0.6966 (4.2)	-0.2168 (3.6)	2756

Stress	0.2958 (4.3)	-1.0605 (1.3)	0.3447 (2.8)	-0.3781 (6.6)	0.7209 (0.8)	-0.2151 (4.4)	2717
Exercise	0.347 (22.3)	-1.064 (1.0)	0.3826 (7.9)	-0.4897 (38.1)	0.7985 (9.9)	0.0906 (140.3)	2941

Table 2

Power Calculations

Hazard Ratio	Reference Hazard	Follow-up Time (cycles)	Total Time (cycles)	N	Power
0.2	0.040	8	8	460	>0.999
0.3	0.040	8	8	460	>0.999
0.4	0.040	8	8	460	0.986
0.5	0.040	8	8	460	0.914
0.6	0.040	8	8	460	0.725
0.7	0.040	8	8	460	0.457
0.8	0.040	8	8	460	0.223
0.9	0.040	8	8	460	0.089
1.1	0.040	8	8	460	0.085
1.2	0.040	8	8	460	0.186
1.3	0.040	8	8	460	0.343
1.4	0.040	8	8	460	0.526
1.5	0.040	8	8	460	0.696
1.6	0.040	8	8	460	0.827
1.7	0.040	8	8	460	0.912
1.8	0.040	8	8	460	0.960

Table 3

Characteristics of N=470 Women in the Mount Sinai Study of Women Office Workers in Three Categories of Daily Caffeine Servings

	0 to 1 serving N=118 N (%)	>1 to 2 servings N=133 N (%)	>2 servings N=219 N (%)	Chi-square *p*-value
Age (years)[a]				
19-24	15 (12.7)	10 (7.5)	16 (7.3)	0.05
25-29	44 (37.3)	49 (36.8)	57 (26.0)	
30-34	37 (31.4)	46 (34.6)	81 (37.0)	
35-41	22 (18.6)	28 (21.1)	65 (29.7)	
Body mass index (kg/m^2)[a]				
<20	27 (22.9)	20 (15.2)	33 (15.1)	0.53
20-25	52 (44.1)	72 (54.6)	116 (53.0)	
25.1-30	23 (19.5)	24 (18.2)	44 (20.1)	
>30	16 (13.6)	16 (12.1)	26 (11.9)	
Missing	0	1	0	
Race				
Non-Hispanic white	91 (77.1)	92 (69.2)	185 (84.5)	0.02
Non-Hispanic black	16 (13.6)	25 (18.8)	16 (7.3)	
Hispanic	5 (4.2)	10 (7.5)	7 (3.2)	
Other	6 (5.1)	6 (4.5)	11 (5.0)	
Marital status[a]				
Single	36 (30.5)	44 (33.1)	47 (21.5)	0.04
Married	78 (66.1)	80 (60.2)	151 (69.0)	
Separated, divorced, widowed	4 (3.4)	9 (6.8)	21 (9.6)	

Highest education[a]				
High school or less	16 (13.7)	22 (16.5)	44 (20.1)	0.006
Tech school or some college	38 (32.5)	46 (34.6)	100 (45.7)	
College grad and higher	63 (53.9)	65 (48.9)	75 (34.3)	
Missing	1	0	0	
Cigarettes (mean per day)[b]				
0	81 (71.1)	95 (72.5)	105 (48.8)	<0.0001
0-9	27 (23.7)	28 (21.4)	61 (28.4)	
10-20	6 (5.3)	7 (5.3)	27 (12.6)	
>20	0 (0.0)	1 (0.8)	22 (10.2)	
Missing	4	2	4	
Alcohol (mean drinks per day)[b]				
0	23 (20.2)	11 (8.4)	18 (8.4)	0.001
≤1	36 (31.6)	33 (25.2)	49 (22.2)	
>1	55 (48.3)	87 (66.4)	148 (68.8)	
Missing	4	2	4	
Trying to get pregnant[a]				
No	77 (72.6)	99 (79.2)	156 (74.6)	0.48
Yes	29 (27.4)	26 (20.80)	53 (25.4)	
Missing	12	8	10	
Mean frequency of unprotected sex per ovulatory window[b]				
0	25 (21.9)	28 (21.4)	39 (18.1)	0.55
<1	19 (16.7)	34 (26.0)	55 (25.6)	
1-4	44 (38.6)	40 (30.5)	72 (33.5)	
<4	26 (22.8)	29 (22.1)	49 (22.8)	
Missing	4	2	4	
Ever used oral birth control[a]				
No	23 (20.5)	27 (20.8)	30 (13.9)	0.16
Yes	89 (79.5)	103 (79.2)	186 (86.1)	
Missing	6	3	3	
Parity[a]				
0	51 (43.2)	47 (35.3)	70 (32.0)	0.33
1	31 (26.3)	39 (29.3)	63 (28.8)	
2+	36 (30.5)	47 (35.3)	86 (39.3)	

Conceived during study				
No	63 (55.3)	84 (64.1)	136 (63.3)	0.28
Yes	51 (44.7)	47 (35.9)	79 (36.7)	
Missing	4	2	4	
Mean cycle length (days)[b]				
21 to 25	9 (8.0)	19 (15.0)	23 (10.8)	0.31
26 to 35	87 (77.0)	97 (76.4)	165 (77.5)	
36 to 113	17 (15.0)	11 (8.7)	25 (11.7)	
Missing	5	6	6	
Mean bleed length (days)[b]				
1 to 5	48 (42.5)	68 (52.3)	111 (51.9)	0.41[c]
5 to 7	63 (55.8)	60 (46.2)	97 (45.3)	
7 to 10	2 (1.8)	2 (1.5)	6 (2.8)	
Missing	5	3	5	
Cycle variability (days)				
1st tertile (0 to 2.1)	22 (23.4)	43 (38.4)	68 (35.6)	0.10
2nd tertile (2.2 to 4)	31 (33.0)	37 (33.0)	62 (32.5)	
3rd tertile (4 to 108.2)	41 (43.6)	32 (28.6)	61 (31.9)	
Missing	24	21	28	
Mean stress (on a scale of 1: low stress, to 4: high stress)[b]				
0 to 1.75	42 (38.2)	47 (36.2)	62 (29.3)	0.40
1.75 to 2.36	32 (29.1)	45 (34.6)	79 (37.3)	
2.36 to 4	36 (32.7)	38 (29.2)	71 (33.5)	
Missing	8	3	7	
Exercise (% of days per cycle)[b]				
0% to 9%	38 (33.3)	36 (27.9)	77 (36.3)	0.48
10% to 29%	38 (33.3)	43 (33.3)	71 (33.5)	
30% to 100%	38 (33.3)	50 (38.8)	64 (30.2)	
Missing	4	4	7	

[a] At the onset of the study

[b] Mean over study duration

[c] Fisher's exact *p*-value

Table 4

Characteristics of N=460 Women in the Mount Sinai Study of Women Office Workers in Three Categories of Daily Coffee Servings

	0 servings	>0 to 1 serving	>1 servings	Chi-square *p*-value
	N=88	N=178	N=194	
	N (%)	N (%)	N (%)	
Age (years)[a]				
19-24	13 (14.8)	16 (9.0)	11 (5.7)	0.001
25-29	31 (35.2)	68 (38.2)	47 (24.2)	
30-34	31 (35.2)	57 (32.0)	74 (38.1)	
35-41	13 (14.8)	37 (20.8)	62 (32.0)	
Body mass index (kg/m^2)[a]				
<20	10 (11.4)	35 (19.8)	34 (17.5)	0.13
20-25	43 (48.9)	83 (46.9)	108 (55.7)	
25.1-30	23 (26.1)	31 (17.5)	34 (17.5)	
>30	12 (13.6)	28 (15.2)	18 (9.3)	
Missing	0	1	0	
Race				
Non-Hispanic white	66 (75.0)	127 (71.4)	169 (87.1)	0.0001
Non-Hispanic black	15 (17.1)	33 (18.5)	6 (3.1)	
Hispanic	2 (2.3)	8 (4.5)	12 (6.2)	
Other	5 (5.7)	10 (5.6)	7 (3.6)	
Marital status[a]				
Single	22 (25.0)	51 (28.7)	50 (25.8)	0.47
Married	59 (67.1)	119 (66.9)	126 (65.0)	
Separated, divorced, widowed	7 (8.0)	8 (4.5)	18 (9.3)	

Highest education[a]				
High school or less	10 (11.4)	33 (18.5)	38 (19.6)	0.45
Tech school or some college	35 (39.8)	67 (37.6)	78 (40.2)	
College grad and higher	43 (48.9)	78 (43.8)	78 (40.2)	
Cigarettes (mean per day)[b]				
0	64 (72.7)	118 (66.3)	99 (51.0)	0.0003
0-9	21 (23.9)	41 (23.0)	54 (27.8)	
10-20	3 (3.4)	14 (7.9)	23 (11.9)	
>20	0 (0.0)	5 (2.8)	18 (9.3)	
Alcohol (mean drinks per day)[b]				
0	23 (26.1)	18 (10.1)	11 (5.7)	<0.0001
≤1	23 (26.1)	53 (29.8)	42 (21.7)	
>1	42 (47.7)	107 (60.1)	141 (72.7)	
Trying to get pregnant[a]				
No	55 (69.6)	116 (69.9)	153 (82.3)	0.01
Yes	24 (30.4)	50 (30.1)	33 (17.7)	
Missing	9	12	8	
Mean frequency of unprotected sex per ovulatory window[b]				
0	19 (21.6)	33 (18.5)	40 (20.6)	0.36
<1	17 (19.3)	36 (20.2)	55 (28.4)	
1-4	31 (35.2)	62 (34.8)	63 (32.5)	
<4	21 (23.9)	47 (26.4)	36 (18.6)	
Ever used oral birth control[a]				
No	23 (27.7)	27 (15.6)	29 (15.1)	0.03
Yes	60 (72.3)	146 (84.4)	163 (84.9)	
Missing	5	5	2	
Parity[a]				
0	43 (48.9)	63 (35.4)	59 (30.4)	0.05
1	18 (20.5)	51 (28.7)	62 (32.0)	
2+	27 (30.7)	64 (36.0)	73 (37.6)	

Conceived during study				
No	49 (55.7)	92 (51.7)	142 (73.2)	<0.0001
Yes	39 (44.3)	86 (48.3)	52 (26.8)	
Mean cycle length (days)[b]				
21 to 25	12 (14.5)	20 (11.6)	19 (10.1)	0.20
26 to 35	57 (68.7)	138 (80.2)	144 (76.6)	
36 to 113	14 (16.9)	14 (8.1)	25 (13.3)	
Missing	5	6	6	
Mean bleed length (days)[b]				
1 to 5	35 (40.2)	88 (49.7)	104 (53.9)	0.23[c]
5 to 7	51 (58.6)	84 (47.5)	85 (44.0)	
7 to 10	1 (1.2)	5 (2.8)	4 (2.1)	
Missing	1	1	1	
Cycle variability (days)				
1st tertile (0 to 2.1)	24 (33.3)	48 (32.0)	61 (34.7)	0.98
2nd tertile (2.2 to 4)	24 (33.3)	49 (32.7)	57 (32.6)	
3rd tertile (4 to 108.2)	24 (33.3)	53 (35.3)	57 (32.6)	
Missing	16	28	19	
Mean stress (on a scale of 1: low stress, to 4: high stress)[b]				
0 to 1.75	34 (39.5)	63 (36.0)	54 (28.3)	0.14
1.75 to 2.36	30 (34.9)	62 (35.4)	64 (33.5)	
2.36 to 4	22 (25.6)	50 (28.6)	73 (38.2)	
Missing	2	3	3	
Exercise (% of days per cycle)[b]				
0% to 9%	31 (36.1)	55 (31.1)	64 (33.5)	0.65
10% to 29%	32 (37.2)	58 (32.8)	62 (32.5)	
30% to 100%	23 (26.7)	64 (36.2)	65 (34.0)	
Missing	2	1	3	

[a] At the onset of the study

[b] Mean over study duration

[c] Fisher's exact *p*-value

Table 5

Characteristics of N=460 Women in the Mount Sinai Study of Women Office Workers in Three Categories of Daily Tea Servings

	0 servings N=87 N (%)	>0 to 1 serving N=325 N (%)	>1 servings N=48 N (%)	Chi-square *p*-value
Age (years)[a]				
19-24	8 (9.2)	27 (8.3)	5 (10.4)	0.49
25-29	28 (32.2)	108 (33.2)	10 (20.8)	
30-34	29 (33.3)	117 (36.0)	16 (33.3)	
35-41	22 (25.3)	73 (22.5)	17 (35.4)	
Body mass index (kg/m^2)[a]				
<20	16 (18.4)	56 (17.2)	7 (14.9)	0.85
20-25	42 (48.3)	168 (51.7)	24 (51.1)	
25.1-30	20 (23.0)	57 (17.5)	11 (23.4)	
>30	9 (10.3)	44 (13.5)	5 (10.6)	
Missing	0	0	1	
Race				
Non-Hispanic white	71 (81.6)	254 (78.2)	37 (77.1)	0.46[c]
Non-Hispanic black	7 (8.1)	42 (12.9)	5 (10.4)	
Hispanic	5 (5.8)	16 (4.9)	1 (2.1)	
Other	4 (4.6)	13 (4.0)	5 (10.4)	
Marital status[a]				
Single	19 (21.8)	92 (28.3)	12 (25.0)	0.02
Married	56 (64.4)	218 (67.1)	30 (62.5)	
Separated, divorced, widowed	12 (13.8)	15 (4.6)	6 (12.5)	

Highest education[a]				
High school or less	17 (19.5)	58 (17.9)	6 (12.5)	0.83
Tech school or some college	35 (40.2)	124 (38.2)	21 (43.8)	
College grad and higher	35 (40.2)	143 (44.0)	21 (43.8)	
Cigarettes (mean per day)[b]				
0	54 (62.1)	199 (61.2)	28 (58.3)	0.29[c]
0-9	19 (21.8)	86 (26.5)	11 (22.9)	
10-20	6 (6.9)	29 (8.9)	5 (10.4)	
>20	8 (9.2)	11 (3.4)	4 (8.3)	
Alcohol (mean drinks per day)[b]				
0	16 (18.4)	30 (9.2)	6 (12.5)	0.21
≤1	20 (23.0)	85 (26.2)	13 (27.1)	
>1	51 (58.6)	210 (64.6)	29 (60.4)	
Trying to get pregnant[a]				
No	64 (82.1)	226 (73.9)	34 (72.3)	0.29
Yes	14 (18.0)	80 (26.1)	13 (27.7)	
Missing	9	19	1	
Mean frequency of unprotected sex per ovulatory window[b]				
0	26 (29.9)	56 (17.2)	10 (20.8)	0.08
<1	16 (18.4)	76 (23.4)	16 (33.3)	
1-4	24 (27.6)	119 (36.6)	13 (27.1)	
<4	21 (24.1)	74 (22.8)	9 (18.8)	
Ever used oral birth control[a]				
No	11 (13.3)	61 (19.2)	7 (14.9)	0.39
Yes	72 (86.8)	257 (80.8)	40 (85.1)	
Missing	4	7	1	
Parity[a]				
0	29 (33.3)	122 (37.5)	14 (29.2)	0.14
1	21 (24.1)	99 (30.5)	11 (22.9)	
2+	37 (42.5)	104 (32.0)	23 (47.9)	

Conceived during study				
No	56 (64.4)	190 (58.5)	37 (77.1)	0.04
Yes	31 (35.6)	135 (41.5)	11 (22.9)	
Mean cycle length (days)[b]				
21 to 25	5 (6.0)	42 (13.4)	4 (8.7)	0.30
26 to 35	66 (78.6)	237 (75.7)	36 (78.3)	
36 to 113	13 (15.5)	34 (10.9)	6 (13.0)	
Missing	3	12	2	
Mean bleed length (days)[b]				
1 to 5	45 (51.7)	149 (46.3)	33 (68.8)	0.04[c]
5 to 7	39 (44.8)	166 (51.6)	15 (31.3)	
7 to 10	3 (3.5)	7 (2.2)	0 (0.0)	
Missing	0	3	0	
Cycle variability (days)				
1st tertile (0 to 2.1)	22 (31.0)	97 (34.2)	14 (33.3)	0.84
2nd tertile (2.2 to 4)	22 (31.0)	96 (33.8)	12 (28.6)	
3rd tertile (4 to 108.2)	27 (38.0)	91 (32.0)	16 (38.1)	
Missing	16	41	6	
Mean stress (on a scale of 1: low stress, to 4: high stress)[b]				
0 to 1.75	27 (32.5)	110 (34.3)	14 (29.2)	0.17
1.75 to 2.36	21 (25.3)	115 (35.8)	20 (41.7)	
2.36 to 4	35 (42.2)	96 (29.9)	14 (29.2)	
Missing	4	4	0	
Exercise (% of days per cycle)[b]				
0% to 9%	30 (35.3)	104 (32.3)	16 (34.0)	0.62
10% to 29%	28 (32.9)	110 (34.2)	14 (29.8)	
30% to 100%	27 (31.8)	108 (33.5)	17 (36.2)	
Missing	2	3	1	

[a] At the onset of the study

[b] Mean over study duration

[c] Fisher's exact *p*-value

Table 6

Characteristics of N=460 Women in the Mount Sinai Study of Women Office Workers in Three Categories of Daily Cola Servings

	0 servings	>0 to 1 serving	>1 servings	Chi-square *p*-value
	N=57	N=341	N=62	
	N (%)	N (%)	N (%)	
Age (years)[a]				
19-24	3 (5.3)	28 (8.2)	9 (14.5)	0.29
25-29	16 (28.1)	107 (31.4)	23 (37.1)	
30-34	21 (36.8)	126 (37.0)	15 (24.2)	
35-41	17 (29.8)	80 (23.5)	15 (24.2)	
Body mass index (kg/m^2)[a]				
<20	11 (19.3)	61 (17.9)	7 (11.3)	0.03
20-25	27 (47.4)	182 (53.5)	25 (40.3)	
25.1-30	13 (22.8)	61 (17.9)	14 (22.6)	
>30	6 (10.5)	36 (10.6)	16 (25.8)	
Missing	0	1	0	
Race				
Non-Hispanic white	50 (87.7)	267 (78.3)	45 (72.6)	0.11[c]
Non-Hispanic black	1 (1.8)	43 (12.6)	10 (16.1)	
Hispanic	2 (3.5)	16 (4.7)	4 (6.5)	
Other	4 (7.0)	15 (4.4)	3 (4.8)	
Marital status[a]				
Single	9 (15.8)	96 (28.2)	18 (29.0)	0.22[c]
Married	45 (79.0)	221 (64.8)	38 (61.3)	
Separated, divorced, widowed	3 (5.3)	24 (7.0)	6 (9.7)	

Highest education[a]				
High school or less	10 (17.5)	54 (15.8)	17 (27.4)	0.01
Tech school or some college	19 (33.3)	130 (38.1)	31 (50.0)	
College grad and higher	28 (49.1)	157 (46.0)	14 (22.6)	
Cigarettes (mean per day)[b]				
0	42 (73.7)	208 (61.0)	31 (50.0)	0.09[c]
0-9	11 (19.3)	88 (25.8)	17 (27.4)	
10-20	2 (3.5)	31 (9.1)	7 (11.3)	
>20	2 (3.5)	14 (4.1)	7 (11.3)	
Alcohol (mean drinks per day)[b]				
0	11 (19.3)	34 (10.0)	7 (11.3)	0.26
≤1	12 (21.1)	87 (25.5)	19 (30.7)	
>1	34 (59.7)	220 (64.5)	36 (58.1)	
Trying to get pregnant[a]				
No	38 (71.7)	240 (75.5)	46 (76.7)	0.81
Yes	15 (28.3)	78 (24.5)	14 (23.3)	
Missing	4	23	2	
Mean frequency of unprotected sex per ovulatory window[b]				
0	16 (28.1)	64 (18.8)	12 (19.4)	0.59
<1	11 (19.3)	79 (23.2)	18 (29.0)	
1-4	19 (33.3)	120 (35.2)	17 (27.4)	
<4	11 (19.3)	78 (22.9)	15 (24.2)	
Ever used oral birth control[a]				
No	8 (15.1)	61 (18.3)	10 (16.1)	0.80
Yes	45 (84.9)	272 (81.)	52 (83.9)	
Missing	4	8	0	
Parity[a]				
0	15 (26.3)	132 (38.7)	18 (29.0)	0.16
1	16 (28.1)	98 (28.7)	17 (27.4)	
2+	26 (45.6)	111 (32.6)	27 (43.6)	

Conceived during study				
No	38 (66.7)	205 (60.1)	40 (64.5)	0.56
Yes	19 (33.3)	136 (39.9)	22 (35.5)	
Mean cycle length (days)[b]				
21 to 25	6 (11.5)	39 (11.8)	6 (9.8)	0.99
26 to 35	40 (76.9)	251 (76.1)	48 (78.7)	
36 to 113	6 (11.5)	40 (12.1)	7 (11.5)	
Missing	5	11	1	
Mean bleed length (days)[b]				
1 to 5	28 (50.0)	168 (49.6)	31 (50.0)	0.90[c]
5 to 7	27 (48.2)	162 (47.8)	31 (50.0)	
7 to 10	1 (1.8)	9 (2.7)	0 (0.0)	
Missing	1	2	0	
Cycle variability (days)				
1st tertile (0 to 2.1)	11 (26.2)	103 (34.2)	19 (35.2)	0.79
2nd tertile (2.2 to 4)	16 (38.1)	95 (31.6)	19 (35.2)	
3rd tertile (4 to 108.2)	15 (35.7)	103 (34.2)	16 (29.6)	
Missing	15	40	8	
Mean stress (on a scale of 1: low stress, to 4: high stress)[b]				
0 to 1.75	19 (34.6)	113 (33.6)	19 (31.2)	0.99
1.75 to 2.36	18 (32.7)	116 (34.5)	22 (36.1)	
2.36 to 4	18 (32.7)	107 (31.9)	20 (32.8)	
Missing	2	5	1	
Exercise (% of days per cycle)[b]				
0% to 9%	20 (36.4)	104 (30.8)	26 (42.6)	0.24
10% to 29%	14 (25.5)	118 (34.9)	20 (32.8)	
30% to 100%	21 (38.2)	116 (34.3)	15 (24.6)	
Missing	2	3	1	

[a] At the onset of the study

[b] Mean over study duration

[c] Fisher's exact *p*-value

Table 7

Multivariable Model for the Effect of Caffeine Consumption on Fecundability

	Mean daily caffeine consumption N=470 women (2744 cycles, 109 pregnancies)		
	N	**FOR**[a]	**95 % CI**
Caffeine (servings)			
1 (0 to 1)	118	reference	
2 (>1 to 2)	133	0.62	(0.36 - 1.07)
3 (>2)	219	0.71	(0.44 - 1.15)

[a] Fecundability odds ratio

Table 8

Multivariable Model for the Effect of Coffee Consumption on Fecundability[a]

	Mean daily coffee consumption N=460 women (2740 cycles, 109 pregnancies)		
	N	**FOR**[a]	**95 % CI**
Coffee (servings)			
1 (0)	88	reference	
2 (>0 to 1)	178	1.24	(0.76 - 2.02)
3 (>1)	194	0.33	(0.19 - 0.57)

[a] Fecundability odds ratio

Table 9

Multivariable Model for the Effect of Tea Consumption on Fecundability[a]

	Mean daily tea consumption N=460 women (2740 cycles, 109 pregnancies)		
	N	**FOR[a]**	**95 % CI**
Tea (servings)			
1 (0)	87	reference	
2 (>0 to 1)	325	1.40	(0.90 - 2.19)
3 (>1)	48	0.66	(0.29 - 1.48)

[a] Fecundability odds ratio

Table 10

Multivariable Model for the Effect of Cola Consumption on Fecundability[a]

	Mean daily cola consumption N=460 women (2740 cycles, 109 pregnancies)		
	N	**FOR[a]**	**95 % CI**
Cola (servings)			
1 (0)	57	reference	
2 (>0 to 1)	341	1.89	(1.11 - 3.22)
3 (>1)	62	0.75	(0.34 - 1.67)

[a] Fecundability odds ratio

CURRICULUM VITAE

Emily K. Steinmetz

Home: 1021 Walter Ave
Louisville, KY 40215
502-938-5187
esteinmetz8@gmail.com

1) Education

2015-Present **University of Louisville**, Louisville, KY
Enrolled in the Master of Science in Epidemiology program
Projected graduation in May 2017

Relevant courses: Public Health in the U.S., Statistical Foundations for Epidemiology, Epidemiologic Methods, Theoretical Foundations for Epidemiology, Epidemiologic Data Management I & II, Epidemiology of Cardiovascular Disease and Chronic Disease, Population Pathology, Epidemiologic Research Management, Advanced Epidemiologic Methods, Global Information Systems, Hierarchical Linear Modeling.

2001-2005 **Bellarmine University**, Louisville, KY
Bachelor of Arts in Biology
Cum Laude

Relevant courses: Principles of Biology, Plant and Animal Diversity, Quantitative Methods in Biology, Cell Biology, Microbiology, Vertebrate Physiology, Molecular Biology, Ecology, Genetics, Introductory Chemistry I & II, Intermediate Chemistry I & II, Biochemistry I, Calculus I & II, Physics I & II.

2) **Work Experience**

2016-Present **Graduate Research Assistant,** *University of Louisville*
Department of Epidemiology and Population Health
Supervisor: Kira Taylor, PhD
Responsible for recruiting clinical patients for a fertility study. Recruitment includes explaining the study and its risks and benefits, obtaining informed consent, addressing questions and concerns, collecting questionnaires and urine samples, and activating prepaid gift

cards. Analyze urine samples using ELIZA and real time PCR. Conduct preliminary statistical analysis of data. Assisted with the Institutional Biosafety Committee application.

2015-2016 **Graduate Research Assistant,** *University of Louisville*
Diabetes and Obesity Center
Supervisor: Timothy O'Toole, PhD
Processed and analyzed human blood samples through CBC and flow cytometry. Utilized the FreezerPro database to manage stored samples and print labels for sample collection.

2010-2015 **Research Technologist II,** *University of Louisville*
Diabetes and Obesity Center
Supervisor: Daniel Conklin, PhD
Responsible for mouse colony maintenance and management, including tracking breeders, determining genoypes through PCR and managing the mLIMS database. Performed phenotype tests using the TSE Phenomaster Physiological Cage System, the Lunar PIXImus densitometer, and through glucose tolerance tests and insulin tolerance tests. Responsible for maintaining genotyping and phenotyping equipment and for training personnel and students in genotyping and phenotyping methods. Attended a ten-day Metabolic Syndrome Course at Vanderbilt University in the summer of 2011.

2007-2010 **Associate Chemist,** *CreoSalus*
Advanced ChemTech, Peptide Department
Supervisor: Thomas Hopkins, PhD
Performed manual synthesis of peptides and amino acids, operated automated synthesizers, purified peptides on HPLC systems, and helped in the preparation of the company safety manual.
Advanced ChemTech, Quality Control
Supervisor: Mark Jacobi
Responsible for analyzing product purity by HPLC, mass spec, IR, and TLC, and preparation certificates of analysis. Entered data into Microsoft Access database.

2007 **Temporary Worker,** *University of Louisville*
Hormone Receptor Laboratory, Biochemistry Department
Supervisor: James Wittliff, PhD
Responsible for staining histological slides, and for purifying DNA, RNA and protein. Entered patient data into Microsoft Access database.

2005-2006 **Teaching Assistant,** *Miami University*
Taught undergraduate zoology labs (vertebrate physiology and human physiology). Responsible for lab setup, instruction, preparing and administering exams, and grading papers and exams.

3) Research Experience

2016-Present	**Department of Epidemiology and Public Health, University of Louisville** *Research Advisor: Kira Taylor, PhD* Conducting statistical analysis of a longitudinal dataset to determine the association of various factors with fecundability.
2005-2006	**Zoology Department, Miami University** *Research Advisor: Alan Cady, PhD* Conducted preliminary research on the behavior of harvestmen.
2004-2005	**Biology Department, Bellarmine University** *Research Advisor: William Tietjen, PhD* Conducted senior thesis research on the effects of pesticides on the behavior of ladybug beetles and jumping spiders.
2003	**KBRIN, University of Kentucky** *Research Director: John Rawls, PhD* Entered a competition and won a ten week internship through the Kentucky Biomedical Research Infrastructure Network. Conducted genetic research on Drosophila and presented the results at the Kentucky Academy of Science at Western Kentucky University in the fall of 2004.

4) Honors and Awards

2005	Graduated Cum Laude, Bellarmine University
2002-2005	Cited in the Dean's List for the Spring 2002, Fall 2003, Fall 2004 and Spring 2005 semesters for a GPA of 3.50 or higher.
2001-2005	Monsignor Horrigan Scholarship: academic scholarship requiring the maintenance of a GPA of 3.00 or higher.

5) Publications

Haberzettl, P., Conklin, D., **Steinmetz, E.**, and Bhatnagar, A. *Age-Dependent Insulin Resistance in Aldose Reductase-Null Mice.* Circulation 2011;124:A13129.